

**UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS**

ASTELLAS INSTITUTE FOR REGENERATIVE )  
MEDICINE, and STEM CELL & REGENERATIVE )  
MEDICINE INTERNATIONAL, INC., )

Plaintiffs,

V.

IMSTEM BIOTECHNOLOGY, INC., XIAOFANG WANG, and REN-HE XU,

Defendants.

[illegible]

C.A. NO. 1:17-cv-12239-ADB

**ORAL ARGUMENT REQUESTED**

**DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF THEIR  
MOTION FOR LEAVE TO FILE AMENDED COUNTERCLAIMS**

## **INTRODUCTION**

Pursuant to Fed. R. Civ. P. 15 and 16(b)(4), defendants ImStem Biotechnology, Inc., Ren-He Xu, and Xiaofang Wang (collectively, the “Defendants”) move for leave file amended counterclaims to: (1) add one count under 35 U.S.C. § 256 that Drs. Xu and Wang should be added as named inventors to U.S. Patent No. 8,962,321 (the “321 Patent”); and (2) add Dr. Xu to the existing counterclaim concerning inventorship of U.S. Patent No. 8,961,956 (the “956 Patent”) and expand certain factual allegations relating to that patent.

As set forth below, good cause exists for the proposed amendments. First, the schedule, nature, and course of discovery demonstrate that Defendants have been reasonably diligent. Second, there is room in the schedule. Discovery is ongoing. Despite the parties’ efforts, several depositions remain open; the remaining schedule already requires adjustment. The Court has not yet set a dispositive motion, pretrial conference, or trial date. Third, these proposed amendments involve the same facts, witnesses, documents, and technology as the current claims. To the extent any additional discovery is needed, it is minimal and can be done at the same time the remaining outstanding discovery. Finally, Astellas Institute for Regenerative Medicine and Stem Cell & Regenerative Medicine International, Inc. (collectively, “Plaintiffs”) will not be prejudiced.

## **FACTUAL BACKGROUND**

### **I. Nature of the Dispute<sup>1</sup>**

This is an inventorship dispute arising from the parties’ once-amicable scientific collaboration in the development of protocols for making, and methods of using, mesenchymal

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<sup>1</sup> Because the Court is familiar with the dispute from the parties’ prior papers and the Court’s decision denying Plaintiffs’ motion to dismiss (Dkt. 37) this summary focuses on the issues pertinent to this motion.

stem cells (“MSCs”). Compl. (Dkt. 1) ¶ 9. MSC’s are quasi-differentiated cells that have the ability to become a wide range of bodily cells, such as bone, fat, and cartilage. While less pluripotent than human embryonic stem cells (“hESC”), they retain the ability to change and develop into a wide range of cell types. Prior to 2010, scientists had developed a variety of ways of making a variety of types of MSCs.<sup>2</sup>

In or about 2010, Dr. Kimbrel (who worked for the Plaintiffs) developed a protocol – essentially a recipe – for making a new kind of MSC derived from hemangioblasts (“hemangioblast-derived MSCs” or “HB-MSCs”).<sup>3</sup> Dr. Kimbrel’s protocol was based on a protocol previously developed and published by her colleague Dr. Shi-Jiang Lu, with a few changes to additives and timing such that the protocol as modified appeared to yield MSCs.

In July 2010, Drs. Lu (who worked for the Plaintiffs at the time), Xu, and Wang met to discuss a potential collaboration. During that meeting, Drs. Xu and Wang proposed (and in a subsequent email Dr. Wang again suggested) that they test the effectiveness of MSCs to treat autoimmune disease – Dr. Wang’s area of expertise. Countercl. (Dkt. 20) ¶¶ 18-20. Drs. Wang and Xu specifically proposed multiple sclerosis. *Id.*

The collaboration began and the Defendants’ experiments started yielding results in the early winter of 2010. *See id.* ¶ 24. During the course of the collaboration, Drs. Wang and Xu began making their own substantial modifications to the HB-MSC protocol – including changing the first step, adding glycogen synthase kinase-3 inhibitor, irradiating the resulting cells, and chemically “characterizing” the cells.

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<sup>2</sup> MSCs until that time had been derived from bone marrow, adipose tissues, umbilical cord blood, or directly from hESCs.

<sup>3</sup> The science of cell differentiation involves plating hESCs in petri dishes along with certain nutrients and other chemicals, allowing them to grow, and then successively extracting them from the petri dish, plating them anew (often with a different mix of nutrients and chemicals), and repeating the process until the cells change or “differentiate” into a desired cell type.

On November 30, 2011, Dr. Kimbrel (and other of Plaintiff’ employees) filed provisional patent Application No. 61/656,358 (“provisional application”) – without informing Drs. Wang or Xu, and without listing Drs. Wang, Xu, or Lu as inventors. *Id.* ¶¶ 26, 35. The application claimed methods of making HB-MSCs as well as their use to treat multiple sclerosis and other diseases. *Id.* ¶ 34; Ex. 1 (provisional application) at 49-50.<sup>4</sup>

During prosecution, the provisional application was subjected to a “restriction requirement” by the U.S. Patent & Trademark Office (the “PTO”), which divided the claims into two groups: (i) claims concerning the recipe for *making* the HB-MSCs; and (ii) claims directed to methods of *using* any such cells to treat *inter alia* autoimmune diseases. The former ultimately issued as the ‘321 patent. The latter ultimately issued as the ‘956 patent.<sup>5</sup> *See generally* Answer Ex. A (Dkt. 20-1) (’956 Patent) at 1.

In parallel, Drs. Xu and Wang filed a patent application on their new version of the HB-MSc protocol. It issued as U.S. Patent No. 9,745,551 (the “’551 Patent”).<sup>6</sup>

## II. Procedural History

On November 13, 2017, Plaintiffs filed a complaint alleging that Dr. Kimbrel and fellow Astellas employee Robert Lanza were the true inventors of the ‘551 Patent, and sought a correction of inventorship under 35 U.S.C. § 256 (to replace Drs. Wang and Xu with Drs. Kimbrel and Lanza) as well as relief under a variety of state-law claims for the same conduct.

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<sup>4</sup> The only data the provisional application cited regarding the functionality of HB-MSCs in treating disease was the data received from Dr. Wang. *See* Countercl. ¶ 26.

<sup>5</sup> More precisely, the Plaintiffs filed a continuation-in-part application claiming priority to the ‘358 application (No. 13/691,349). During prosecution of *that* application, the PTO issued the restriction requirement. The Plaintiffs elected to drop the “use” claims from that application and pursue them instead in a new application (No. 13/905,526). The former (No. 13/691,349) became the ‘321 Patent. The latter (No. 13/905,526) became the ‘956 Patent.

<sup>6</sup> Defendants have offered to add Drs. Kimbrel and Lanza as additional co-inventors to the ‘551 Patent, but are unwilling to acquiesce to Plaintiffs’ demand that they remove themselves from the patent (which would make Drs. Kimbrel and Lanza the sole inventors of the ‘551 Patent).

(Dkt. 1). On January 10, 2018, Defendants answered. Dr. Wang counterclaimed that he was an inventor of the '956 patent, seeking a correction of inventorship under 35 U.S.C. § 256 to be added as a named inventor. (Dkt. 33). Dr. Xu (living in Macau) originally joined in the Answer but not the Counterclaim. *Id.*<sup>7</sup>

On October 16, 2018, the Court entered a scheduling order with set out deadlines for initial disclosures, motions to amend pleadings or join parties (October 29, 2018), completion of fact discovery (March 8, 2019), and opening expert reports, rebuttal expert reports, and expert depositions. (Dkt. 44). On January 30, 2019, the parties started producing documents. Thereafter, the parties sought to extend fact, and in some instances, expert discovery. *See* Dkts. 50, 56, 67.

Discovery is still ongoing and will likely not be completed for a few weeks. Although document discovery was slated to end June 28, 2019 (Dkt. 56), the most recent document production was on July 19, 2019. Likewise, although the parties asked the Court to extend depositions until July 19, 2019 (Dkt. 67), several depositions were not completed during that time. Within the past few days, Plaintiffs have informed Defendants that: (1) former employee Dr. Lu is now willing to be deposed on July 26, 2019; and (2) Astellas is willing to make a corporate designee available in response to Defendants' Second 30(b)(6) notice (served on May 31, 2019). Plaintiffs are also taking a four-hour deposition of Dr. Wang on July 29, 2019 (his second one).<sup>8</sup> All parties have also acknowledged the need to delay the start of expert discovery.

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<sup>7</sup> Plaintiffs filed a motion to dismiss Dr. Wang's counterclaims (Dkt.21), which the Court denied on September 28, 2018. (Dkt. 37). Plaintiffs filed their Answer to Dr. Wang's Counterclaims on October 12, 2018. (Dkt. 42).

<sup>8</sup> Dr. Wang's second deposition will be limited to regarding recently-produced documents (after his first deposition) and the attached proposed amended counterclaims. The parties are also attempting to agree on the amount of time Astellas' 30(b)(6) designee will be made available.

The parties have a status conference with the Court on July 23, 2019, and Court has not set a schedule for dispositive motions, a pretrial conference, or trial.

### **III. Defendants' Proposed Amendments**

Defendants seek to add a counterclaim to correct inventorship of the '321 Patent by adding both Drs. Wang and Xu to that patent. Drs. Wang and Xu made at least two significant contributions to the '321 Patent: (1) the invention of mitotically inactivating (e.g. by irradiation) the HB-MSCs described in Claim 14 (Claims 17 & 18); and (2) the invention of comparing HB-MSC potency to bone-marrow derived mesenchymal stromal cells (BM-MSCs) (Claim 21). Defendants also seek to add Dr. Xu to the existing counterclaim (Counterclaim Count I) concerning the '956 Patent and to expand on the underlying factual allegations. In addition to contributing the core concept of using HB-MSCs to treat autoimmune diseases such as multiple sclerosis (previously outlined in Counterclaim Count I), Drs. Xu and Wang made other significant contributions, including mitotically inactivating the HB-MSCs (Claim 5), characterizing the IL-6 secretions in the HB-MSCs (Claim 9), and identifying immune regulatory potency greater than that of bone-marrow-derived MSCs.<sup>9</sup>

In short, if the current motion is allowed the inventorship claims in this case will be: (1) Drs. Kimbrel and Lanza are trying to displace Wang and Xu's "making" patent (the '551); (2) Drs. Wang and Xu are trying to get onto Drs. Kimbrel and Lanza's "making" patent (the '321); and (3) Drs. Wang and Xu are trying to get onto Drs. Kimbrel and Lanza's "using" patent (the '956).

### **LEGAL STANDARDS**

Federal Rule of Civil Procedure 15 provides that "[t]he court should freely give leave [to

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<sup>9</sup> Clean and blacklined versions of the proposed Amended Counterclaims as attached hereto as Exhibits A and B, respectively.

amend’ when justice so requires.” *Mulder v. Kohl’s Dep’t Stores, Inc.*, 865 F.3d 17, 20 (1st Cir. 2013). The Court may deny leave to amend “when the request is characterized by undue delay, bad faith [or] the absence of due diligence on the movant’s part.” *Id.* Where, as here, a motion to amend is filed after the deadline for such motions in the Scheduling Order, “the liberal default rule is replaced with the more demanding ‘good cause’ standard of Fed. R. Civ. P. 16(b).” *Steir v. Girl Scouts of the USA*, 383 F.3d 7, 12 (1<sup>st</sup> Cir. 2004). The rationale behind the good cause standard is that it provides courts with the “devices necessary to manage [their] docket[s]” and facilitates “effective case management.” *See O’Connell v. Hyatt Hotels of Puerto Rico*, 357 F.3d 152, 154 (1st Cir. 2004) (internal quotations omitted); *see also O’Leary v. New Hampshire Boring, Inc.*, 323 F.R.D. 122, 125-26 (D. Mass. 2018) (finding moving party had been diligent, despite passage of time, because *inter alia* it was impractical to hold them to deadline in scheduling order, given the course of discovery and the conduct of the case). Trial courts are granted “great latitude in carrying out case-management functions.” *Ivymedia Corp. v. Ilikebus, Inc.*, 233 F.Supp.3d 228, 230 (D. Mass 2017). Courts often consider efficiency and case management when deciding whether to allow a motion to amend the pleadings. *See, e.g., id.*

## **ARGUMENT**

### **IV. Defendants Have Been Reasonably Diligent**

As the First Circuit has explained, the Court’s exercise of discretion in a leave to amend analysis is context-specific. *See Nikitine v. Wilmington Trust Co.*, 715 F.2d 388, 390 (1st Cir. 2013) (in addressing district court’s decision on a motion for leave to amend, stating that “everything depends on context”); *ACA Fin. Guar. Corp. v. Advest, Inc.*, 512 F.3d 46, 57 (1st Cir. 2008) (“[i]n assessing delay, “[e]ach case ... turn[s] on its own circumstances”).

Here, the context demonstrates reasonable (albeit delayed) diligence and good faith by the Defendants. ImStem is a small company of eight scientists and lab technicians with no

revenue, minimal in-house bandwidth for managing counsel, and no experience with patent litigation. The legal concept of joint inventorship was beyond their ken, even with the assistance of counsel. Joint inventorship “is one of the muddiest concepts in the muddy metaphysics of patent law.” *Dana-Farber Cancer Inst., Inc. v. Ono Pharm. Co.*, 379 F. Supp. 3d 53, 82 (D. Mass. 2019) (quoting *Mueller Brass Co. v. Reading Indus., Inc.*, 352 F. Supp. 1357, 1372 (E.D. Pa. 1972)). Furthermore, the history of the relevant collaboration was (and is) complex.

The Defendants were therefore poorly positioned to determine the precise scope of their counterclaims early in the case, and even as late as of October 28, 2019 (the date for amendment without motion).<sup>10</sup> As of that date, no documents had been produced, no interrogatories had been served, and no depositions had been taken place. It was not until January 30, 2019 that Plaintiffs produced documents that, when read in conjunction with Defendants’ documents, confirmed that it was Drs. Xu and Wang – and not the Plaintiffs – who first conceived of the idea behind “mitotically inactivating” the HB-MSCs. *See, e.g.*, AIRM00049689, AIRM00049403, AIRM00015422, AIRM00015421; *see also, e.g.*, IMSTEM-0007426-27, IMSTEM-0001788-1802, IMSTEM-0005291, IMSTEM-0005351-52.<sup>11</sup> Plaintiffs did not produce the lab notebooks of the key witnesses until February and March, 2019. It took time to go through these (and other) dense technical materials among the 300,000 pages that Astellas produced, and depositions of the authors (in June and July, 2019) provided insight into what was (and was not) written in them. In addition, it was not until preparing for depositions with Dr. Xu – who lives in

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<sup>10</sup> Although the deadline for discovery was extended several times, the deadline for amending the pleadings was not also extended. In retrospect, setting a deadline for amendment before fact discovery even started was premature, which was compounded by the extension of fact discovery, as well as the “end of discovery” status conference with the Court (which is set for July 23, 2019). (Dkts. 50, 56, 67, 69).

<sup>11</sup> The parties designated all of these documents as “Highly Confidential” under the Protective Order; Defendants cannot describe them in this public filing. Because the substance of those documents is not the central issue for this motion – undue delay and prejudice are – Defendants did not think it necessary to describe them. If the Court wishes to see the documents, however, Defendants would be happy to file them under seal.



Macau and was difficult to communicate with before he came to the United States for his July 3, 2019 deposition – that Defendants fully understood the nature and extent of his and Dr. Wang’s inventive contributions to the ‘321 and ‘956 Patents.<sup>12</sup> It was only as Plaintiffs pressed the case, more invasively than the Defendants had expected, that the factual basis for the proposed Amended Counterclaims was uncovered and analyzed.

#### **V. The Timing of the Amendment Will Not Seriously Prejudice Plaintiffs**

The timing of the amendment will not seriously prejudice Plaintiffs. Fact discovery is ongoing. There were several scheduling issues that prevented all the depositions from being complete by July 19, 2019. Plaintiffs have only recently agreed to present Dr. Lu – a former employee of Astellas, represented by the same counsel. Plaintiffs have not yet produced a 30(b)(6) witnesses regarding damages and state law claims (although they have indicated that they are willing to do so). Defendants have also agreed to allow Plaintiffs to take a second (four hour) deposition of Dr. Wang to ask him about recently-produced documents and the proposed counterclaims.<sup>13</sup> Expert discovery has not started. There is no deadline for dispositive motions. Pretrial conference and trial has not been set. In short, the case schedule already needs to be moved, and allowing Defendants to file their proposed counterclaims will not extend the case substantially, if at all.

Nor does the proposed amendment substantially alter the relevant facts in the case. With

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<sup>12</sup> Clean and blacklined versions of the proposed Amended Counterclaims as attached hereto as Exhibits A and B, respectively.

<sup>13</sup> Defendants noticed depositions in May and sought Dr. Lu’s deposition in June. Plaintiffs informed Defendants by letter on July 15, 2019 that they were representing Dr. Lu and proposed a date for his deposition. In the same letter, Plaintiffs asked for a second deposition of Dr. Wang the afternoon of July 23, 2019 (after the status conference with the Court). The parties have since agreed to June 26 for Dr. Lu and July 29 for Dr. Wang.

respect to the ‘321 Patent, the underlying facts are essentially the same.<sup>14</sup> The technology (HB-MSCs) is the same. The ‘321 Patent arises from the same collaboration that gave rise to the ‘551 and ‘956 Patents, both of which are already in suit. Its claims are nearly identical to the claims of the ‘551 Patent (so much so that the PTO forced the Defendants to overcome the ‘321 Patent application during prosecution, *see* Compl. ¶ 48). It is a sibling to the ‘956 Patent, and it shares the same inventors. *Compare* ‘956 patent with ‘321 patent. The “invention story” – at least on Plaintiffs’ side – for the ‘956 and ‘321 Patents is the same. *See, e.g.*, Dkt. 1 at ¶ 29 (“... Erin Kimbrel, with input from [Robert] Lanza, developed a novel method for making a particular type of stem cell (mesenchymal stem cell).”). That common “invention story” has already been the subject of extensive document and deposition discovery. The witnesses, the documents, and the fact discovery that has been conducted to date are all the same. For example, the Kimbrel, Lanza, and Wang lab notebooks exchanged by the parties to establish inventive contribution to the ‘551 and ‘956 Patents are the same ones relevant to the ‘321 Patent. Further, because of the overlap between the ‘321 Patent and the existing allegations in this case regarding the ‘551 Patent – *i.e.* who came up with the process for making HB-MSCs – all of the relevant documents have been sought for, and produced. At most, the only additional discovery needed would be a short deposition of Dr. Wang (already scheduled for July 29, 2019).

The amendments to the ‘956 Patent counterclaim are much the same. Plaintiffs have long known their claim to exclusive invention for that patent was being challenged. Defendants are merely seeking to expand the factual allegations to their existing claim by adding two additional grounds – one a carbon copy of the basis for the ‘321 Patent relating to “mitonically

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<sup>14</sup> Prior to Dr. Xu’s deposition, Defendants told Plaintiffs that they were planning on seeking leave to add an inventorship counterclaim for the ‘321 Patent, told them the factual basis for such a claim, and allowed Plaintiffs to ask Dr. Xu about it during his deposition.

inactivating” cells and one relating to IL-6 (which has been the subject of documents and depositions for months). These factual allegations, while updated for notice purposes, do not themselves change the relief sought: correction of inventorship. Adding Dr. Xu as an additional person who should be a named inventor on the ‘956 Patent would also not require any additional discovery; his claim to inventorship is identical to Dr. Wang’s, as both men jointly developed the inventive contributions to the ‘956 Patent.<sup>15</sup>

In sum, the Defendants are not asking for new documents, not asking for more interrogatories, and are not asking for additional witnesses.

## **VI. The Amendment Promotes Judicial Economy**

Perhaps the best illustration of how allowing Defendants’ motion would promote judicial efficiency, husband the parties’ resources, and, ultimately lead to less (not more) delay is to consider the alternative. If Defendants are not allowed to file Amended Counterclaims, they would certainly be able to file a new action with the same allegations. Because of the overlap in technology and this Court’s familiarity with the issues in this case, it would make sense to identify it as a related action to this case. If that new case was not joined to this action, it would mean that the parties (and the Court) would, in essence, litigate the same case twice.<sup>16</sup>

Because Defendants’ proposed counterclaims would require only a minimal extension of fact discovery (which is already contemplated), would not postpone the trial (which has not been scheduled), and would not be a “major alteration” in trial tactics and strategy, Defendants respectfully request that the Court grant their motion.

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<sup>15</sup> The only other Defendant witness that the Plaintiffs have sought is ImStem’s part-time, nominal CEO, Michael Men. Mr. Men is an investor and businessman in the Chinese metal business. He has testified that he played no role in inventing anything in this case.

<sup>16</sup> Defendants’ statements are regarding judicial efficiency and husbanding the parties’ resources, not whether any claim regarding the ‘321 Patent should be considered permissive or compulsory.

### **CONCLUSION**

The early delays in this case were the result of Plaintiffs' filing an (unsuccessful) motion to dismiss. Fact discovery did not get going in earnest until early 2019 and is not yet complete. Case development and understanding of the issues does not happen all at once; it takes review of documents, preparing witnesses for deposition, and taking depositions to develop a complete picture. Defendants' proposed additional counterclaim does not inject additional facts or legal theories that have not already been pursued by the parties. Furthermore, the absence of dispositive motion, pretrial, and trial dates means that adjusting the only remaining deadline (expert discovery) – that all parties acknowledge will need to be moved to account for unfinished discovery – means that Defendants should be able to pursue their proposed amended counterclaims so that the parties (and the Court) can most efficiently address all aspects of this dispute at once.

**WHEREFORE**, for the aforementioned reasons, Defendants respectfully request that the Court allow them to file their proposed Amended Counterclaims.

Dated: July 22, 2019

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that this document filed through the CM/ECF system will be sent electronically to the registered participants as identified on the NEF and paper copies will be sent to those indicated as nonregistered participants on July 22, 2019.

Dated: July 22, 2019

/s/ Timothy R. Shannon

Timothy R. Shannon